CHAPTER 2

METHODS

Research context: the Perinatal Project Groningen (PPG)

This thesis is part of an ongoing program on the etiology of emotional and behavioural disorders run at the Department of Social Psychiatry, University of Groningen. The study benefits from the Perinatal Project Groningen (PPG), a birth cohort started in order to study associations between factors operating during gestation and in the perinatal period on the one hand, and the child's postnatal condition on the other. For this purpose, all births of singleton infants in the years 1975-1978 in the University Hospital Groningen (n = 3162) were documented in great detail. Obstetric data were collected on precoded lists and stored on computer file. They included data on social background, past pregnancies (e.g. preterm deliveries, abortions, previous infertility), non-obstetric condition of the mother during present pregnancy, obstetric aspects of present pregnancy (e.g. pre-eclampsia, hypertension, weight gain), parturition, and the child's immediate postnatal condition. For subsamples, follow-up data on childhood neurological condition, school performance and behavioural and emotional problems were available. The present study is a continuation of PPG as a large-scale study of longitudinal development in the Netherlands.

Predictor variables: The obstetric optimality score (OOS)

Prenatal, perinatal, and postnatal conditions were quantified using the so-called 'optimality scores' that were introduced by Prechtl[1] and Touwen and colleagues[2]. The basic idea of the optimality concept is that it is easier to define an 'optimum' condition than a 'normal' one. For example, while multiparity implies a less optimal obstetrical condition compared to nulliparity, it is unclear where to draw the distinction between "normal" and "abnormal" parity. However, an optimal parity is easier to define: having given birth to one previous child is optimal.

Touwen and collegues[2] constructed a list of 74 items describing the pre- and perinatal condition of the mother and the foetus (see Appendix). This list was based on common-sense clinical experience and contemporary literature on risk factors for perinatal death and cerebral palsy[1]. For each item an optimum was

defined, and each optimal condition contributed a point, yielding a sum score ranging between 0 (least optimal) and 74 (most optimal). The lower the total score in an individual case, the less optimal the course of pregnancy and/or delivery is assumed to have been. As items were not individually weighed, the scores were quantitative indicators of how many items were not optimal. As it turned out empirically, suboptimality of most of the important items (like low birth weight) was associated with a simultaneous lack of optimality in many others. This would suggest that the system is self-weighing[1].

Interesting research results have been obtained by applying the optimality concept to analyses of the effects of a particular complication[1]. For instance, infants of hypertensive and/or alcoholic mothers were more likely than others to be neurologically abnormal if their optimality score was relatively low. Findings like these have supported the clinical impression that complications do not necessarily operate as risk factors if they occur in splendid isolation. The optimality concept demonstrates this, puts it to quantitative use and is, moreover, easily applicable. However, it should be clear that in clinical use as well as in research an optimality list should never replace the separate recording of complications. Complications and clinical diagnoses on the one hand, and obstetrical optimality scores on the other, are complementary to each other and not mutually exclusive.

Subjects and sampling

Original subjects

Original subjects were 3162 singleton infants, born in the years 1975-78 in the University Hospital Groningen. Perinatal data of these children were documented in detail.

Sample followed up at school age

Subsamples of the PPG birth cohort were re-examined when the children were aged between 5.5 and 11 years.

The subsamples consisted of:

- all children with a definitely abnormal neonatal neurological condition (n = 133)[3]
- a random sample of all children with a normal neonatal neurological condition (n = 300) or a mildly abnormal neonatal neurological condition (n = 293)[3]
- all children born preterm and/or small for gestational age between 1 January 1977 and 30 June 1978 (n = 237)[4]
- all children born at term who participated in a study on the effect of intrauterine exposure to ritodrine[5]. Ritodrine has been shown to not affect affect neurobehavioural development in this cohort.[5]

Attrition in the various subsamples varied from 0 to 7%. Children with overt neurological syndromes such as cerebral palsy were excluded from the present analyses. Because of some overlap in the subsamples the total number of children re-examined between age 5.5 and 11 years was 1186. For a subsample of 580 children who were in primary school (i.e. >6 years), school performance was assessed.

Sample followed up at 20-25 years: questionnaires

When the cohort had reached the age bracket 20 years – 25 years, 92% (n = 2900) was alive and tracked down as living in the Netherlands. All these cohort members were sent a questionnaire pack focusing on emotional and substance use problems in young adulthood. Almost 60% (n = 1826) completed and returned the questionnaire pack.

Sample followed up at 20-25 years: psychiatric interview

Of 682 subjects (24%) full data for the three age brackets (perinatal, primary school age, and young adulthood) were available. From these, 258 study subjects (8% of full sample, 38% of subjects with full data) were selected for a psychiatric diagnostic interview on the basis of their *Obstetric Optimality Score.* For this purpose, the group of 682 subjects with full data available was divided into deciles. Originally, the aim was to select 32 persons at random from every decile, so that the total group selected for psychiatric interview would be 320. However,

as less than 32 persons were available in the highest and in the three lowest deciles, individuals falling in the more central 6 deciles had to be oversampled. Table 2.1 shows the number of cohort members available in the OOS-deciles and the number of individuals who responded to the invitation to partake in the interview.

Table 2.1: PPG cohort members available in OOS-deciles and number of persons interviewed

Decile	OOS-score	Number of persons available	Number of persons interviewed	Percentage
1e	42-44	1	1	100%
2e	45-47	13	9	69%
3e	48-50	26	20	77%
4e	51-53	59	35	59%
5e	54-56	89	36	40%
6e	57-59	137	37	27%
7e	60-62	151	35	23%
8e	63-65	132	40	30%
9e	66-68	64	35	55%
10e	69-71	10	10	100%
Total		= 682	= 258	Percentage

Samples and predictor variables

Table 2.2 shows scores for the different samples and the total PPG-sample for some important predictor variables and possible confounders studied in this thesis. The mean perinatal condition of the study groups was less optimal compared to the remainder of the PPG-cohort: Obstetric optimality scores were lower, maternal smoking during pregnancy occurred more often, birth weight and Apgar scores were lower, and age of the mother was higher in the study groups. Moreover, pregnant women attending the Department of Obstetrics of the Groningen University Hospital are not a random selection of the pregnant

population but have relatively more complicated pregnancies.[6] The Netherlands is a country with a high proportion of home deliveries (40% in the years 1975-78), and only women with poor obstetric histories and serious complications of pregnancy were referred to the Department of Obstetrics for advanced perinatal care.

Table 2.2: Chapters of the thesis, sampling, and predictor variables

Predictor variable	**Chapter 3, 4 &5:** Follow up at 5.5-11 years **n = 1186**	**Chapter 6:** Follow up at 20-25 years: Questionnaires Data available perinatally, at primary school age, and young adulthood) **n = 682**	**Chapter 8:** Follow up at 20-25 years: Psychiatric interview **n = 258**	**Total PPG Cohort** **N = 3162**
Obstetric Optimality Score (OOS)	59.2 (4.8)	59.3 (5.1)	58.6 (6.2)	60.1 (4.6)
Maternal smoking during pregnancy	4.9 (6.9)	4.3 (6.6)	4.2 (6.7)	4.5 (6.8)
Breast vs bottle feeding	30 : 70%	32 : 68%	34 : 66%	33 : 67%
Birth weight	3103g (631)	3102g (647)	3143 (698)	3300 (565)
Apgar score 3 minutes	9.3 (1.3)	9.2 (1.4)	9.1 (1.5)	9.5 (1.1)
Age of the mother during pregnancy	25.6 (4.8)	26 (4.8)	26 (4.9)	25.4 (4.7)
Married vs unmarried status of the parents during pregnancy	94 : 6%	96 : 4%	91 : 9%	93 : 7%
Socio-economic status of the parents during pregnancy (low: middle: high)	33 : 33 : 34%	30 : 33 : 37%	27 : 33 : 40%	35 : 34 : 31%

The relatively high rate of adverse perinatal conditions can be considered as an advantage in a study on associations between obstetrics on the one hand and childhood school performance and behaviour and psychopathology in young adulthood on the other. However, it should be borne in mind that reported incidences of abnormalities can not be extrapolated to the general population.

Follow-up at school age (5.5-11 years)

The re-assessment at school age consisted of 1) a detailed neurological examination, 2) behavioural questionnaires, and 3) school performance tests.

The detailed neurological examination[7] focused on the presence of minor neurological dysfunctions (MND). These dysfunctions are also known as soft neurological signs, but the term minor neurological dysfunction is preferable as the word "soft" has the fallacious connotation of ambiguity.[8] Essential to the diagnosis of MND is the presence of a *cluster* of signs of dysfunctions. This means that the presence of a single sign of dysfunction, such as the isolated presence of a Babinski sign, does not allow for the label MND. The signs of MND were divided into six clusters (Table 2.3), which are organised according to the functional, neurobehavioural subsystems of the nervous system used in clinical practice.

The person carrying out the neurological examination was unaware of the child's perinatal history, its behavioural development and its school performance. The presence or absence of dysfunction in these clusters can be rated with substantial interobserver agreement.[9]

As regards childhood behaviour, parents and teachers were asked to indicate, on a 7-item questionnaire, whether they regarded the child in question as more, the same or less *irritable, hyperactive, difficult to handle, headstrong, easily frightened, shy,* and *anxious* than the average child. No data could be obtained from 0.3% of the parents and 7.2% of the teachers.

Table 2.3 Functional clusters of MND, based on the neurological examination of Touwen[7], adapted from Hadders-Algra et al.[3] The clusters were developed on the basis of clinical knowledge.[7]

Cluster	Based on	Criteria for dysfunction
1. Dysfunctional muscle tone regulation	Muscle tone Posture during lying, sitting, standing, and walking	One or more of the following: - consistent mild deviations in muscle tone - consistent mild deviations in posture
2. Reflex abnormalities	Abnormal intensity and/or threshold or asymmetry in: - biceps reflex - knee jerk - ankle jerk Footsole respons: uni- or bilateral babinski sign	Presence of at least two signs
3. Choreiform dyskinesia	- Spontaneous motor behaviour - Test with extended arms - Face, eyes, tongue	Presence of at least one of the following: - Marked choreiform movements of distal and facial muscles - Slight or marked choreiform movements of proximal muscles, eyes or tongue
4. Coordination problems	- Finger-nose test - Fingertip-touching test - Diadochokinesis - Kicking - Knee-heel test - Reaction to push (sitting, standing) - Romberg - Tandem gait - Standing on one leg	Presence of age-inadequate performance on at least two tests
5. Fine manipulative disability	Finger-opposition test: - smoothness - transition Follow-a-finger test Circle test	Presence of age-inadequate performance on at least two tests
6. Rarely occurring miscellaneous dysfunctions	- Motor behaviour of face, eyes, pharynx, tongue - Associated movements during diadochokinesis, finger-opposition test, walking on toes or heels	Evidence of at least one of the following: - mild cranial nerve palsy - excessive amount of associated movements (for age)

For a subsample of 580 children who were in primary school, reading, spelling, and arithmetic were assessed with short standardized Dutch tests. Reading was assessed by counting the number of test-words the child could read aloud correctly within one minute.[10] Similarly, arithmetic was evaluated by counting the number of standard-problems the child could solve correctly within three minutes.[11] Spelling was tested by assessing how many dictated words out of a standard list of 50 words, the child could write correctly.[12] Also, for this subgroup (n=580), concentration (good, moderate, poor), distractibility (little, moderate, severe), and attention span (long, moderate, short) were scored by teachers and parents.

Follow-up at age 20-25

Questionnaires

The self-report questionnaire, sent to cohort members when they were 20-25 years old, consisted of socio-demographic factors, the short version of the General Health Questionnaire (GHQ12, Koeter & Ormel[13]), the depression and anxiety scales of the Symptom Checklist (SCL-90[14]), and questions on alcohol, cigarette and drug use in the last month and the last year.

Sociodemographic variables

As to socio-demographic variables other than age and gender, information was gathered on marital state, education, job or study (yes/no), and nationality. Of the 1726 respondents 53.1% was female. Mean age was 22.3 years (SD= 1.15, range 20-26). Only 0.3% did not have the Dutch nationality. Eight percent did not work or study, because they were houseman or housewife (2.6%), unemployed (3.7%), or unable to work (1.6%). Thirty percent of the respondents were married of living with a steady partner, and 3.7% only had primary school.

General Health Questionnaire (GHQ)

The General Health Questionnaire is a general measure of psychological distress and consisted of 60 items in its original form (Goldberg[15]). The short Dutch version of the GHQ, the GHQ-12, was tested extensively by Koeter and Ormel.[13]

The GHQ concentrates on two fundamental groups of problems: inability to carry out one's normal "healthy" functions and the appearance of new phenomena of a distressing nature. The patient is asked to assess changes in his/her mood, feelings and behaviour during the last month. The patient evaluates their occurrence on a 4-point response scale ranging from: "less than usual", "no more than usual", "rather more than usual", "much more than usual". The standard scoring method recommended by Goldberg[15] is called the "GHQ-method". Scores for the first two response categories are "0" and for the two others "1". Sometimes a modified scoring method, called Goodchild and Duncan-Jones's method (CGHQ), is used.[16] In this way of scoring the answer depends on whether the positive answer to a question indicates illness or health. Among items indicating illness, like "feeling unhappy and depressed", a respondent gets 1 point for the answer "no more than usual". Therefore, the scoring of answers for such questions is 0,1,1,1. In items indicating health, like "being able to concentrate on whatever you're doing", the reply "same as usual" has a 0-value. The scoring of items indicating health is then the same as the standard scoring in the GHQ (0,0,1,1). Both scoring methods give the same theoretical range of sum scores, which is between 0 and 12 points for the GHQ-12. In the analyses carried out in this thesis, the original method of response scoring of Goldberg was used (0,0,1,1).

In population studies women generally have higher mean GHQ-scores than men.[13] For the most part this difference is probably due to the higher prevalence of anxiety and depressive symptoms in women. Furthermore, there seems to be a gender difference in the effects of aging for GHQ-scores: for men there is no age effect, while for women GHQ-scores tend to decrease with aging. Table 2.4 shows mean scores for males and females aged 18-24 years in the general Dutch population[13] and scores of respondents in this thesis. Finally, gender related reporting biases might be responsible for the gender difference in

GHQ-scores.[17]

Table 2.4: Mean GHQ-12 scores and standard deviations (between brackets) in the general Dutch population aged between 18 and 24 (Koeter & Ormel[13]) and in this thesis

	General Dutch population	Subjects in this thesis
Males	1.20 (2.18)	1.44 (2.63)
Females	1.68 (2.15)	2.46 (3.24)

Symptom Checklist-90 (SCL-90)

The Dutch translation[14] of the Symptom Checklist-90[18] is a self-report of subjects' symptoms and psychopathological features on 8 subscales: Paranoid ideation and interpersonal sensitivity, hostility, sleeping problems, insufficient thinking and acting, somatisation, agoraphobia, anxiety and depression. Besides, the total sumscore is a general measure of neuroticism.

The Dutch version of the SCL-90 resembles the original questionnaire of Derogatis and colleagues[18] as much as possible. When answering the questions the respondent reports, on a five point scale, the extent to which, during the last week, he or she suffered 'not at all'(1), 'a little' (2), 'fairly' (3), 'rather much' (4) or 'a great deal' (5) from the symptom at issue. The SCL-90 proved to be valid and reliable in the Dutch population.[14]

In this thesis, two subscales of the SCL-90 were used: anxiety and depression. Anxiety is scored on a 10-item subscale concerning symptoms that are clinically associated with a high level of anxiety. It concerns complaints related to general symptoms as nervousness and tension, along with more specific symptoms like panic attacks and restlessness. Finally, cognitive problems such as expectations of disaster and fearful thoughts and ideas are addressed.

The depression scale of the SCL-90 consists of 16 items addressing symptoms that are usually associated with the clinical syndrome of "depression". Among these are complaints like dejection, inability to enjoy things, lowered self-esteem, and thoughts of guilt, hopelessness, death and suicide, as well as physical aspects like loss of appetite, lack of energy, and decreased sexual interest.

Table 2.5a shows normative scores for the depression and anxiety subscales of the SCL-90[14]. These normative scores are based on scores from 1026 individuals randomly selected from and representative for the general Dutch population (>18years old). Table 2.5b shows mean scores and standard deviations in this population and in the population studied in this thesis.

Table 2.5a: Normative SCL-90 scores in the general Dutch population (n = 1026, 42% males)(Arrindell & Ettema[14])

	Anxiety Males	Females	Depression Males	Females
Very high	22	27	34	42
High	15-21	18-26	23-33	28-41
Upwards of mean	12-14	14-17	21-22	23-27
Mean	11	13	18-20	21-22
Downwards of mean	10	11-12	17	19-20
Low	10	10	16	17-18
Very low	10	10	16	16

Table 2.5b: mean scores and standard deviations (between brackets) for the anxiety and depression scale of the SCL-90 in the general Dutch population (Arrindell & Ettema[14]) and in the subjects studied in this thesis

	Anxiety Males	Females	Depression Males	Females
General Dutch population n = 1026	13.0 (4.3)	14.6 (5.7)	20.7 (6.3)	23.8 (8.6)
Subjects studied in this thesis n = 1826	12.3 (4.2)	14.0 (5.5)	21.2 (7.9)	24.7 (9.9)
Two-tailed t-test	T = 4.2 $p < 0.001$	t = 2.8 p = 0.006	t = -1.7 p = 0.082	t = -2.4 p = 0.015

Questions on alcohol, cigarette and drug use

Drug use was assessed with one question: did you use drugs in the last 12 months, like marihuana, amphetamines, cocaine, heroine, etcetera? Subjects could answer with 'never in the past 12 months', '1-4 times', '5-8 times', '9-12 times', or 'more than 12 times'. Table 2.6a shows self-reported drug use by our respondents in the preceding 12 months.

Table 2.6a Self-reported drug use (marihuana, amphetamines, cocaine, heroine, etcetera) in the past 12 months

	Males (n = 807)	**Females (n = 915)**
Never	76.6%	89.5%
1 - 4 times	9.4%	5.0%
5 – 8 times	1.4%	0.7%
9 – 12 times	2.3%	0.7%
more than 12 times in the past 12 months	10.2%	4.2%

Alcohol use was assessed with three questions: how many glasses of alcohol did you drink in the past 30 days ('never', 'less than one glass a day', '1-3 glasses a day', '4-7 glasses a day', 7-12 glasses a day', or 'more than 12 glasses a day'), how many glasses of alcohol did you drink in the past 12 months (idem), how many times were you drunk in the past 12 months ('never', '1-4 times', '5-12 times', 13-20 times', or 'more than 20 times in the past 12 months')? Tables 2.6b and 2.6c show selfreported alcohol use in the preceding 30 days and 12 months and number of times drunk in the preceding 12 months. For comparison, in the general Dutch population 10.7% of the males and 13.1% of the females in this age category had never used alcohol in the preceding month.[19]

Table 2.6b Self-reported alcohol use in the past 30 days and in the past 12 months

	Males (n = 804)		**Females (n = 913)**	
	past 30 days	*past 12 months*	*past 30 days*	*past 12 months*
Never	12.7%	9.0%	31.5%	19.2%
< 1 glass a day	46.9%	46.5%	52.7%	61.4%
1-3glasses a day	31.4%	34.2%	12.5%	14.9%
4-7glasses a day	7.3%	8.6%	2.5%	3.5%
7-12glasses a day	0.9%	0.9%	0.4%	0.7%
>12 glasses a day	0.9%	0.9%	0.3%	0.3%

Table 2.6c Self-reported times of drunkenness in the past 12 months

	Males	**Females**
Never	40.5%	67.9%
1 - 4 times	37.1%	24.8%
5 – 12 times	12.3%	5.1%
13 – 20 times	5.6%	1.8%
more than 20 times	4.6%	0.4%

Cigarette smoking was assessed with two questions: 1) How many cigarettes a day did you smoke in the past 30 days (number of cigarettes a day)? and 2) How many cigarettes a day did you smoke in the past 12 months ('none', 'less than 3 cigarettes a day', 3-10 cigarettes a day', '11-20 cigarettes a day', or more than 20 cigarettes a day)? Among males who had smoked in the preceding 30 days, mean number of cigarettes smoked was 12.1 (range 1-40, SD 6.6), for females this was 11.2 cigarettes (range 1-40, SD 7.1). Table 2.6d shows frequencies of cigarette smoking of our respondents in the preceding 12 months. For comparison, in the general Dutch population 40.3% of the males and 35.1% of the females in this age category had never smoked in the preceding month.[19] Among male smokers in the general Dutch population mean number of cigarettes smoked in the preceding month was 10.6, for females this was 9.8.[19]

Table 2.6d Self-reported cigarette smoking in the past 12 months

	Males (n = 794)	**Females (n = 906)**
Never	47.5%	50.7%
< 3 cigarettes a day	7.2%	8.8%
3-10 cigarettes a day	19.0%	16.8%
11-20 cigarettes a day	22.2%	18.9%
> 20 cigarettes a day	4.2%	4.9%

Psychiatric interview

The Composite International Diagnostic Interview (CIDI) was developed in the 1980s in the context of a joint project of the World Health Organisation and the US Alcohol, Drug Abuse and Mental Health Administration (ADAMHA).[20] It was worked out mainly from the point of view of epidemiologic studies of psychopathology in the general population. The CIDI is a comprehensive, highly structured and standardised interview, allowing diagnosis of mental disorders in accordance with criteria of ICD-10[21] and DSM-IV[22]. The interview covers the following 12 sections, dedicated to individual groups of disorders:

- Nicotine dependence
- Somatisation and dissociative disorders
- Anxiety disorders
- Depression and dysthymic disorder
- Mania and affective, bipolar disorder
- Schizophrenia and other psychotic disorders
- Eating disorders
- Alcohol related disorders
- Obsessive-compulsive disorder
- Disorders related to psychoactive substances abuse
- Mental deterioration (dementia, memory disorder, and other cognitive disorders)
- Posttraumatic stress disorders.

In the present study, the computerized Dutch translation version 1.1 (validated by Smeets and Dingemans[23] was used to obtain DSM-IV diagnosis.[22] The interviews were carried out by 3 interviewers trained at a university hospital in Amsterdam, the Netherlands. We focused on six groups of disorders:

- depressive disorders
- anxiety disorders and phobias
- somatisation
- alcohol abuse and/or dependence
- substance use, including cannabis and sedatives
- nicotine dependence.

Prevalence of CIDI-diagnoses for these groups of psychiatric disorders in 258 PPG-cohort members in the preceding 12 months are shown in table 2.7a. Table 2.7b shows the multimorbidity distribution.

Table 2.7a: Prevalence of 12 month CIDI-diagnoses in 258 PPG-cohort members

	Males (n = 128)	Females (n = 130)
Depression	9.4%	15.4%
Anxiety	6.3%	10.0%
Somatisation	0.8%	3.1%
Alcohol abuse and/or dependence	12.5%	3.8%
Substance use	7.0%	1.5%
Nicotine dependence	11.7%	9.2%

Table 2.7b Multimorbidity distribution of six types of psychiatric disorders in a sample of 258 PPG-cohort members

Multimorbidity	Males (n = 128)	Females (n = 130)
0 disorders	74.2%	71.5%
1 disorder	14.8%	19.2%
2 disorders	4.7%	7.7%
3 disorders	3.1%	0.8%
4 disorders	2.3%	0.8%
5 disorders	0.8%	0.0%

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